

Committed To A Cure

2010-2011 ANNUAL REPORT



New Research. New Treatments. **NEW HOPE.**

ALS
THERAPY ALLIANCE



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THE ALS THERAPY ALLIANCE BOARD MEMBERS ARE PROFOUNDLY GRATEFUL TO CVS/PHARMACY FOR ITS ALS FUNDRAISING CAMPAIGN, WHICH HAS BEEN INVALUABLE IN THE EFFORT TO DEVELOP AN INTERNATIONAL CONSORTIUM OF ALS RESEARCHERS.”

ROBERT H. BROWN, JR., D.PHIL., M.D.

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Members of the CVS/pharmacy team present a check to the ALS Therapy Alliance's Researching a Cure Campaign for \$4.3 million. Pictured from left to right is a Red Sox bat girl; Larry Merlo, President and Chief Operating Officer of CVS Caremark; Jon Roberts, Executive Vice President, Rx Purchasing, Pricing and Network Relations for CVS Caremark Corporation; Kevin Turner of the Kevin Turner Foundation and 2011 co-chair; Dr. Robert Brown, President of the ALS Therapy Alliance; Dr. Merit Cudkowicz, Board of Directors, ALS Therapy Alliance; Dr. Larry Hayward, Board of Directors, ALS Therapy Alliance; Dr. H. Robert Horvitz, Board of Directors, ALS Therapy Alliance; Treg Charlton, 2011 co-chair, Barry Winovich, 2011 co-chair and Red Sox bat girl.

ALS Therapy Alliance MISSION

More than 500,000 people alive today will die of amyotrophic lateral sclerosis (ALS). Each year, another 5,600 Americans are diagnosed with ALS, a fatal, progressive, paralyzing disorder. Today, there is no cure. But there is hope, thanks to promising new research and treatments being conducted by the ALS Therapy Alliance (ATA), that a cure will be available soon. The ATA has galvanized a global team of scientists who are working tirelessly towards a common goal: to find a cure for ALS.

The ATA is pleased to continue their long collaboration with major corporate donor CVS/pharmacy. Through the generosity of CVS/pharmacy colleagues and customers, the ATA has raised more than \$30 million over 11 years for ALS research.

The Facts on ALS

WHAT IS ALS?

ALS is a rapidly progressing neurological disorder that attacks motor nerve cells responsible for voluntary movement. Initially, symptoms of ALS may include twitching, cramping and stiffness of muscles, unusual fatigue and clumsiness, or difficulty swallowing and speaking. Although the sequence of emerging symptoms and the disease's progression differ from person to person, an ALS patient's muscles will ultimately weaken and become paralyzed, but their ability to think, see, hear, smell, taste and touch remain unaffected. Ultimately, when the muscles in the diaphragm and chest wall fail, patients cannot breathe and most will die from respiratory failure, usually four to six years after symptoms begin.

WHAT CAUSES ALS?

The primary problem in ALS is the death of motor neurons and their axons in the spinal cord. When the neuron is damaged, it can no longer control the muscles; this leads to muscle atrophy and ultimately to paralysis of the limbs and an inability to chew, swallow, speak and breathe. The precise cause of ALS is not known, except in some cases of familial ALS, in which specific gene defects cause this disease. Scientists are studying possible causes for non-familial (sporadic) ALS, including environmental factors such as infections or toxins. In both familial and non-familial ALS, data implicate several types of neuronal abnormalities including: inadequate generation of cellular energy, excessive electrical firing, altered metabolism of RNA, defective transport of materials along nerve processes known as axons, and impaired axonal turnover.

ALS AND GENETICS

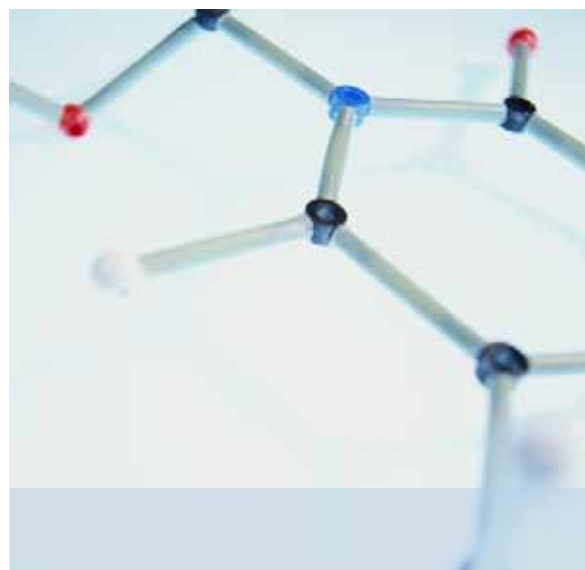
The ATA's state-of-the-art genetic testing techniques are identifying why certain people have the disease. Scientists believe that susceptibility to ALS is strongly influenced by genetic makeup and have identified more than 20 different genes whose defects can trigger the disease. Many of these run in families. Approximately 10% of ALS cases arise because of gene mutations.

For example, some cases of ALS are caused by mutations in a gene that produces a free radical absorbing protein, known as superoxide dismutase (SOD1); mutations in this gene render the SOD1 protein toxic to neurons. Mutations in two other genes, known as FUS/TLS and TDP43, adversely influence the metabolism of cellular RNA, leading to sequestration of these proteins in abnormal locations in motor neurons. It was recently discovered that expansions of a stretch of DNA in a gene called C9orf72 can also cause ALS, sometimes in association with fronto-temporal dementia. (ATA funding helps support the research of one of the scientists who discovered this gene, Dr. Rosa Rademakers.)



The most exciting developments have been in the area of human genetics, where several new familial ALS genes have been identified and now account for the majority of known familial cases of ALS. These new genes provide the basis for mechanistic studies and potential targets for therapy.”

Tom Maniatis, Ph.D.
Director, ALS Therapy Alliance





ATA brings together outstanding researchers and allows them to work together and share their unique areas of expertise. This convergence will greatly accelerate efforts to develop effective therapies for ALS.”

Lawrence J. Hayward, M.D., Ph.D.
Director, ALS Therapy Alliance



Daily Discoveries

An ATA-funded state-of-the-art genomic center at the University of Massachusetts allows application of the latest gene sequencing technology in the search for new ALS genes. The center, in collaboration with investigators at Duke University, is engaged in the process of studying the sequence of all DNA within the full genome of individuals with familial and non-familial ALS.

MOTOR NEURON PROBLEMS IN ALS

Data suggest that motor neurons that develop ALS are afflicted with many defective cellular processes and events; these act together to lead ultimately to motor neuron death. Some of the processes implicated in ALS motor nerves include: excessive electrical activity, insufficient generation of energy because of dysfunction of organelles known as mitochondria, altered RNA metabolism, impaired synthesis of proteins needed for growth of neuronal processes, alterations in the turnover of proteins, and impair transport of materials along the nerve axon (so-called axonal transport). New findings in studies funded by the ATA indicate that in some cases of sporadic ALS (with no mutations in the SOD1 gene or protein), the SOD1 protein gets misfolded and can directly inhibit axonal transport.

TOOLS TO EXPEDITE THE ALS DIAGNOSIS

Over the last year, the ALS Therapy Alliance has sponsored a large, multi-center effort to collect blood and spinal fluid from patients with ALS. Researchers are identifying substances in those fluids that indicate how active the disease process is. Such substances, known as biomarkers, are highly valuable and are expected to provide more sensitive readouts of the response to potential therapies, thereby reducing the costs and accelerating the time course of ALS treatment trials. Also notable about this new program is that researchers will acquire these specimens at frequent intervals from the same patients, providing a high-resolution time course of how the biomarkers change with disease. This study will be among the largest undertaken prospectively to identify new ALS biomarkers.

HEAD INJURIES & ALS

New research suggests that some cases of ALS may be triggered by head injuries, and scientists are now examining the relationship between head trauma and the onset of this disease.

Recent studies of athletes and military personnel have shown higher-than-average ALS diagnoses, possibly caused by concussions and other head trauma that eroded their central nervous systems. In one study, 14 former NFL players were diagnosed with ALS, about eight times higher than average among men of similar ages. Another study of professional Italian soccer players showed that these players developed ALS at rates approximately six times above average.

U.S. military personnel also have higher-than-normal ALS cases, possibly because of head injuries sustained in combat.

Scientists will be continuing to study patients with significant histories of head and brain trauma, looking for clues into the disease and possible new treatment options.

ANIMALS & PETRI DISHES

A critical resource in the process of delineating how diverse abnormalities interrelate, and in defining possible treatments, are ALS models in Petri dishes and in animals, like fruit flies and mice. One powerful approach to generating such models is to build them around the same genetic defects that cause human ALS. For example, development of cell-based and yeast-based ALS models that allow one to test possible drug treatments. As another example, mice can be made to incorporate human ALS genes that are transmitted faithfully in each generation of mice and that cause a form of ALS in mice that strikingly resembles the human disease. These models allow one to dissect molecular and cellular events that underlie ALS and, importantly, to test potential therapies.

Recent ATA studies of mice and fish have led to exciting biomedical research of the neurons, particularly the axon. New discoveries have shown that treating the axon can repair a sick neuron. Previously, extensive work has gone into treating a cell body to prevent destruction, but now ATA experts are exploring how treating the neuron can help block cell degeneration. Today, tests are under way to determine if this approach can suppress cells that carry ALS.

Until recently research in ALS mouse models has focused primarily on mutations in the SOD1 gene. Now, ATA scientists and others are generating new models in mice based on ALS-related mutations in the genes FUS/TLS, TDP43 and C9orf72.

STEM CELL BIOLOGY OF LIVING ALS PATIENTS

Another very powerful approach to studying ALS in cell-based models is through the use of stem cells. Stem cells have an extraordinary capacity to proliferate and also to differentiate into diverse cell types in the body. Accordingly, one can use stem cells to generate not only motor neurons but also the surround cells that nurture motor neurons. An innovative new way to generate disease-specific human neurons is to create induced pluripotent stem (iPS) cells from human fibroblasts. When derived from fibroblasts from ALS cases, these iPS cells are genetically identical to the ALS patients who donated the cells. This provides scientists with an unprecedented opportunity to investigate disease mechanisms and test potential drug therapies using actual human motor neurons. ATA scientists have generated ALS patient-specific iPS cells containing specific genetic mutations — a significant step in the quest for a cure.



The efforts of the ATA involve a striking collaboration among an impressive group of esteemed scientists, each of whom brings special knowledge and a unique perspective to the mission. These interactions are invaluable as we examine ALS from different viewpoints and consider different approaches in our quest for a cure.”

Robert H. Brown, Jr., D.Phil., M.D.
President, ALS Therapy Alliance

A Network of Global Collaboration

“The ATA’s global collaboration supports the most exciting, innovative research. There are several hopeful ALS approaches and treatments in development — ceftriaxone, dexamipexole, NP001 and Cytokinetics compound to name a few.”

Merit E. Cudkowicz, M.D.
Director, ALS Therapy Alliance

The ATA has amassed an impressive constellation of people working together to achieve the common goal of finding therapies for ALS. Teams with various specialties — from biomedical researchers to neurotherapeutics experts to RNA experts — each bring their unique perspective and knowledge to the table. This collaborative approach allows these teams of scientists to more effectively problem-solve and explore new possibilities for future research, experiments and treatments.

The multi-collaborative nature of the ATA program is well represented by research into ALS genetics under the leadership of Prof. Ammar Al-Chalabi at Kings College in London. Dr. Al-Chalabi’s ATA-funded project exploits new technologies in genetics to study very large sets of DNA from ALS cases and controls to identify genetic variants that either increase ALS susceptibility or alter its progression. Additionally, the ATA is supporting investigators in Leuven, Belgium, led by Dr. Wim Robberecht, who are investigating how molecular signals inside motor neurons are activated to promote cell death in ALS. These projects will help illuminate pathways and events that are targets for therapy. Investigators funded by the ATA are also engaged in research into a childhood form of ALS in southern India.

Scientists and clinicians from an array of ALS networks, like those in London and Leuven, meet at regular intervals to discuss their findings and implement new trials. Many of these meetings have received funding through the ALS Therapy Alliance and CVS/pharmacy partnership. These groups include the country’s largest clinical trials network, known as the Northeast ALS (NEALS) study group, the ALS Research Group, and the International Consortium on ALS and Superoxide Dismutase (ICOSA). The ATA believes that financial support for NEALS is critical, as this group is extremely active in conducting ALS clinical research and trials around ALS. NEALS is conducting a number of promising clinical trials, including studies to determine whether creatine (an energy-enhancing substance) and tamoxifen (an estrogen receptor blocking drug) impact neurodegenerative disorders like ALS.

NEW TREATMENTS, NEW HOPE

While there is no cure for ALS, there continues to be important progress in developing and testing new therapies for this disease.

As mentioned above, ATA has helped to support the NEALS Consortium, the largest ALS treatment organization in the world. Funding from the ATA has helped NEALS organize its annual meeting, conduct some drug studies, study ALS biomarkers, and create a database of previous human ALS trials. It is striking that the NEALS team worked with BiogenIdec, Inc., to recruit several hundred individuals with ALS in record time to test the drug dex-pramipexole in a BiogenIdec study.

for ALS Treatments

In other efforts, researchers are working to develop therapies that “turn off” genes whose mutations are toxic to motor neurons. A team led by Dr. Richard Smith and Dr. Don Cleveland (University of San Diego) and Dr. Tim Miller (Washington University), jointly with NEALS and the company Isis, Inc., has started pilot studies in humans of a therapy known as anti-sense oligonucleotides, which will silence the mutant SOD1 gene in patients in whom mutant SOD1 is a causative factor. So far, the pilot phases of this study have demonstrated that the drug is safe.

Trials are under way to improve methods to silence the SOD1 gene in ALS mice. The ALS Therapy Alliance is supporting Dr. Michele Maxwell at Massachusetts General Hospital in the development of a method to turn the ALS gene on or off using oral antibiotics. Several groups are investigating other approaches to silencing the SOD1 gene.

The ATA has provided funding for the laboratory of Dr. Robert Brown, Jr., (University of Massachusetts Medical School) who is working with a team in Worcester, Mass., to develop new ways to deliver silencing elements to the nervous system. Another exciting effort in silencing SOD1 is under way under the direction of Dr. Don Cleveland and Dr. Brian Kaspar (Ohio State University) to use viruses to deliver gene silencing agents to the spinal cord of ALS mice.

ACCELERATING DRUG DISCOVERY

Still another new research technique implemented in many laboratories, including the ATA’s many labs, is a method called high-throughput drug screening. In this approach, scientists test drugs in tiny Petri dish models of ALS, which increases efficiencies and reduces costs. Compounds that appear helpful in high-throughput tests can then be examined more definitively in the animal models and then, ultimately, in human models.

To put this in context, human trials can cost as much as \$5 million and take three years to conduct. Animal trials, such as mouse studies, can cost \$50,000 and take six months to complete. Petri dish models, however, are highly effective and can cost just \$5 and take one day to complete.

CVS/PHARMACY PARTNERSHIP

Working with CVS/pharmacy, the ATA has raised more than \$30 million over the past 11 years. More than 92% of the money raised through this partnership has been earmarked for ALS research. This money has funded more than 100 different ALS research projects and 25 ATA-sponsored conferences globally.



The support of CVS/pharmacy is extraordinary. To my knowledge, no other corporation has ever provided such remarkable support for research to understand and cure ALS. The efforts of CVS/pharmacy colleagues and customers are exemplary and unprecedented; all of us in ALS research are indebted to them for all that they have done.”

Merit E. Cudkowicz, M.D.
Director, ALS Therapy Alliance

Board of Directors

ROBERT H. BROWN, JR., D.PHIL., M.D.



Robert H. Brown, Jr., D.Phil., M.D., earned his bachelor's degree in biophysics at Amherst College, a doctorate of philosophy in neurophysiology at Oxford University, and a medical degree at Harvard Medical School. He is presently the chair of the Department of Neurology at the University of Massachusetts Medical School.

Dr. Brown's primary research interest has been inherited, paralytic neuromuscular disorders with a focus, since 1980, on ALS. He currently serves as the director and organizer of the ALS Therapy Alliance and is a non-voting member on the board.

As part of a consortium of investigators, Dr. Brown played a central role in the discovery of mutations or genetic variants in several ALS-related genes, including cytosolic superoxide dismutase, alsin, dynactin, KIFAP3 and FUS/TLS.

Dr. Brown has also identified gene defects causing three other diseases known as Miyoshi myopathy (dysferlin), hyperkalemic periodic paralysis (skeletal muscle sodium channel), and familial sensory neuropathy (serine palmitoyltransferase).

MERIT E. CUDKOWICZ, M.D., M.SC.



Dr. Merit Cudkowitz is a professor of neurology at Massachusetts General Hospital (MGH) and Harvard Medical School. Dr. Cudkowitz earned her bachelor's of science degree in chemical engineering at the Massachusetts Institute of Technology and completed medical training at the Health Science and Technology Program of Harvard Medical School. She obtained a

master's degree in clinical epidemiology from the Harvard School of Public Health. She was a resident and chief resident in neurology at MGH. She was a fellow in the MGH/Massachusetts Institute of Technology Clinical Investigator Training Program from 1994 to 1996.

Dr. Cudkowitz's research and clinical activities are dedicated to the study and treatment of patients with neurodegenerative disorders, in particular amyotrophic lateral sclerosis (ALS). Dr. Cudkowitz directs the MGH ALS clinic and the MGH Neurology Clinical Trials Unit. She is one of the founders and codirectors of the Northeast ALS Consortium, a group of 92 clinical sites in the United States and Canada dedicated to performing collaborative academic-led clinical trials in ALS. In conjunction with the NEALS consortium, she planned and completed seven multi-center clinical trials in ALS and is currently leading three new trials in ALS. Dr. Cudkowitz received the American Academy of Neurol-

ogy 2009 Sheila Essay ALS award. She has been a pioneer in promoting and developing more efficient methods of testing new therapies in people with ALS. She is actively mentoring young neurologists in clinical investigation in ALS and related neurodegenerative disorders. Dr. Cudkowitz is on the medical advisory board for the Muscular Dystrophy Association and the Amyotrophic Lateral Sclerosis Association.

ROBERT J. FERRANTE, PH.D., M.SC.



Robert J. Ferrante, Ph.D., M.Sc., is a professor of neurology, pathology and laboratory medicine, psychiatry and behavioral neuroscience at the Boston University School of Medicine. He is the director of the Experimental Neuropathology Unit and Translational Therapeutics Laboratory at the Bedford Veterans Affairs Medical Center in Bedford, Mass. Dr. Ferrante has a wide range of knowledge about the neuropathology and

mechanisms of neurodegeneration in adult-onset neurological diseases, especially ALS, with more than 30 years experience in clinical and experimental neurology. He is considered an expert in the application of experimental models of disease and in bench-to-bedside translational studies. Dr. Ferrante is a member of the Northeast ALS Consortium and is a steering committee member on six current human clinical trials using therapeutic agents that were developed in his laboratories. He is currently the director and co-principal proponent of a multi-center phase one clinical trial in ALS for the Veterans Administration.

Over the past 10 years, Dr. Ferrante has developed one of the premier translational programs for developing and characterizing therapeutic strategies for neurological diseases. His laboratory has been a driving force in completing pre-clinical drug trials in mice for direct translation to human clinical trials in ALS patients.

LAWRENCE J. HAYWARD, M.D., PH.D.



Lawrence J. Hayward, M.D., Ph.D., received his doctorate degrees in neuroscience and medicine from Baylor College of Medicine in Houston, Texas. He completed a neurology residency and neuromuscular disease fellowship at Massachusetts General Hospital. During that time, his research focused on neuromuscular conditions caused by defective ion channels. In 2000, Dr.

Hayward started his own laboratory at the University of Massachusetts Medical School as an assistant professor of neurology. Dr. Hayward became an associate professor in 2003 and serves as joint faculty in the departments of physiology, biochemistry and molecular pharmacology, and the program in neuroscience.

He sees patients regularly in the Neuromuscular Clinic and on the wards, contributes to medical school and resident teaching, and serves as a mentor for graduate students and fellows in the laboratory.

In 1998, Dr. Hayward initiated biochemical studies with Dr. Robert Brown to identify toxic properties of mutant SOD1 enzymes that cause familial ALS. Dr. Hayward's group and collaborators have shown that impaired zinc binding and other vulnerabilities produce misfolded forms of the SOD1 protein that are prone to aggregation or other abnormal interactions. Since 2008, the lab has focused upon establishing new in vivo models using mouse and zebrafish systems to investigate mechanisms by which mutant forms of nucleic acid binding proteins cause ALS.

H. ROBERT HORVITZ, PH.D.



H. Robert Horvitz, Ph.D., received the Nobel Prize in Physiology or Medicine in 2002 and is the David H. Koch Professor of Biology at the Massachusetts Institute of Technology (MIT), an investigator of the Howard Hughes Medical Institute, a neurobiologist at the Massachusetts General Hospital, and a member of the MIT McGovern Institute for Brain Research and the

MIT Koch Institute for Integrative Cancer Research. Dr. Horvitz received bachelor's degrees in mathematics and economics from the MIT and performed his Ph.D. studies in biology at Harvard University. Dr. Horvitz was a postdoctoral scientist at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, and has been an assistant, associate and full professor in the Department of Biology at MIT.

Dr. Horvitz has received numerous awards for his accomplishments. Some of these honors include: Charles A. Dana Award for Pioneering Achievement in Health (1995); General Motors Cancer Research Foundation, Sloan Prize (1998); Gairdner Foundation International Award (1999); March of Dimes Prize in Developmental Biology (2000); the Genetics Society of America Medal (2001); the Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience (2001); the Wiley Prize in the Biomedical Sciences (2002); the Peter Gruber Foundation Genetics Prize (2002); the American Cancer Society Medal of Honor (2002); and the Alfred G. Knudson Award of the National Cancer Institute (2005). He has also received several honorary degrees and has served on many editorial boards and committees.

Dr. Horvitz has achieved world-wide recognition for his discoveries of cell death genes and his delineation of the molecular pathways through which these genes operate. These discoveries continue to have new and compelling implications across basic

cell biology and much of medicine, including the fields of cancer and neurodegenerative diseases like ALS.

TOM MANIATIS, PH.D.



Tom Maniatis, Ph.D., is the Isidore S. Edelman Professor and chairman of biochemistry and molecular biophysics at the Columbia University Medical Center. He received his bachelor's degree from the University of Colorado at Boulder and a doctorate in molecular biology from Vanderbilt University.

His postdoctoral studies were carried out at Harvard University and at the Medical Research Council for Molecular Biology in Cambridge, England.

Dr. Maniatis has held research and academic positions at the Cold Spring Harbor Laboratory in New York and the California Institute of Technology in Pasadena, and he recently retired from Harvard University after 30 years on the faculty.

Dr. Maniatis' research has been recognized by numerous awards, including the Eli Lilly Award in Microbiology and Immunology, the Scientific Achievement Award of the American Medical Association, the Richard Lounsbery Award for Biology and Medicine, and the Jacob Heskel Gabbay Award in Biotechnology and Medicine, as well as membership in the U.S. National Academy of Sciences. Dr. Maniatis is best known for pioneering the development and application of recombinant DNA methods to the study of gene regulation. His research has impacted a broad spectrum of biomedical fields, from basic mechanisms of gene expression to advances in understanding human genetic and inflammatory diseases. Dr. Maniatis' laboratory is currently using both mouse and human pluripotent stem cells to study ALS disease mechanisms.

CRAIG C. MELLO, PH.D.



Dr. Craig C. Mello is an investigator at Howard Hughes Medical Institute, the Blais University Chair in Molecular Medicine, and codirector of the RNA Therapeutics Institute at the University of Massachusetts Medical School in Worcester. He received his B.Sc. degree in biochemistry from Brown University in 1982 and received his Ph.D. from Harvard University in 1990. From 1990 to 1994, he conducted postdoctoral

research at the Fred Hutchinson Cancer Research Center in Seattle, Wash.

Board of Directors

Dr. Mello's pioneering research on RNAi, in collaboration with Dr. Andrew Fire, has been recognized with many prestigious awards culminating with the 2006 Nobel Prize in Physiology or Medicine.

Dr. Mello, along with his colleague Dr. Fire, discovered the process by which a particular form of ribonucleic acid – RNA, the cellular material responsible for the transmission of genetic information – can silence targeted genes. This RNAi process offers astounding potential for understanding and manipulating the cellular basis of human disease, and RNAi is now the state-of-the-art method by which scientists can “knock out” the expression of specific genes to thus define the biological functions of those genes. Just as important has been the finding that RNAi is a normal process of genetic regulation that takes place during development, opening a new window on developmental gene regulation.

GREGORY A. PETSKO, D.PHIL.



Gregory Petsko is professor of neurology and neuroscience at Weill Cornell Medical College in New York City and the Tauber Professor of Biochemistry and Chemistry, Emeritus, at Brandeis University. He received a Rhodes Scholarship and obtained his doctorate from Oxford University with Sir David Chilton Phillips in 1973. He is concerned with the three-dimensional structures of proteins and their biochemical func-

tions, especially proteins involved in neurodegenerative diseases. Most of his work is done in collaboration with Brandeis Prof. Dagmar Ringe. He is a member of both the National Academy of Sciences and the Institute of Medicine, as well as the American Academy of Arts and Sciences and the American Philosophical Society. He is a past president of the American Society for Biochemistry and Molecular Biology and president-elect of the International Union of Biochemistry and Molecular Biology. He is coauthor with Dagmar Ringe of the book *Protein Structure and Function*. With her he has trained almost 150 graduate students and postdocs over the past 32 years. He is also the cofounder of two publicly traded biotechnology companies.

His laboratory currently focuses on understanding and developing treatments for ALS, Parkinson's disease and Alzheimer's disease. Using a combination of genetics and biochemistry in a model organism, his group discovered that over expression of the human UPF1 gene can suppress the toxicity of mutant FUS/TLS and mutant TDP-43 in neuronal cell models of ALS. Gene therapy that his group developed based on this discovery is currently being tested in animal models.

As the author of a monthly column in *Genome Biology*, he has a forum for a restless and wide-ranging intellect concerned with scientific and policy issues ranging from the iniquitous influence of impact factors to the effect of mass population shifts, such as our current trend toward a senior-citizen society. He has also written about the scientific basis of the Atkins diet and the importance of the arts and humanities in scientific education. He admits, however, that the columns guest written by his two dogs are much more popular than those he writes himself.

JONATHAN C. ROBERTS



Jonathan C. Roberts is Executive Vice President and COO for CVS Caremark Pharmacy Services. In his current position he is responsible for PBM Trade and Retail Pharmaceutical Purchasing, New Product Development, Underwriting and PBM Networks.

Roberts is a seasoned retail pharmacy executive with more than 30 years of experience in retail pharmacy, 18 of those with CVS Caremark. He is a results-driven, experienced leader with a diverse mix of field management, business operations and information systems integration experience. He most recently served as chief information officer for CVS Caremark, where he spearheaded several key initiatives, including the Pharmacy Service Initiative (PSI). PSI has enhanced pharmacy performance at CVS/pharmacy and has been highlighted in business case studies at the Harvard Business School and Yale School of Management. Roberts is a member of the SureScripts Executive Advisory Council and the eHealth Initiative's Leadership Council. He earned his degree in pharmacy from the Virginia Commonwealth University School of Pharmacy and is a graduate of the Wharton Executive Management Program.

DAVID SCHWARTZ



David Schwartz is a partner with the law firm of Schwartz & Roman PLLC and licensed to practice law in N.H., Mass., Maine, Vt., Fla. and Ga. He received his undergraduate degree from Georgetown University, his law degree from the University of Miami, and his Master of Law degree in Taxation from Boston University. Schwartz assisted in setting up the ALS Therapy Alliance in 2002 and has been its legal counsel and a major supporter since its inception.

2010 Independent Auditor's Report

Cindy Courtney, CPA, CFP®

64 Lafayette Road #7
Post Office Box 887
North Hampton, NH 03862
Tel: 603-964-2988 Fax: 603-964-2987
email: cindy@cv-cpa.com

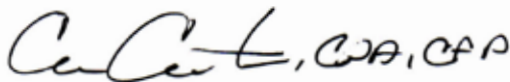
INDEPENDENT AUDITOR'S REPORT

To the Board of Directors
ALS Therapy Alliance, Inc.

I have audited the accompanying statement financial of position of ALS Therapy Alliance, Inc. (a nonprofit organization) as of December 31, 2010, and the related statement of activities and statement of cash flows for the year then ended. These financial statements are the responsibility of the Organization's management. My responsibility is to express an opinion on these financial statements based on my audit.

I conducted my audit in accordance with auditing standards generally accepted in the United States of America. Those standards require that I plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. I believe that my audit provides a reasonable basis for my opinion.

In my opinion, the financial statements referred to above present fairly, in all material respects, the financial position of ALS Therapy Alliance, Inc. as of December 31, 2010, and the changes in net assets, and its cash flows for the year then ended, in conformity with accounting principles generally accepted in the United States of America.



Cindy Courtney, CPA, CFP
North Hampton, NH

February 22, 2011

Money Concepts Financial Planning Centre
All securities through Money Concepts Capital Corp. Member NASD/SIPC
11440 Jog Road, Palm Beach Gardens, FL 33418-3764 Tel: 561-472-2000 email: ccourtney@moneyconcepts.com

Financials 2010

FINANCIAL POSITION

ASSETS		
Cash and cash equivalents (Note #1)	8,351,636	
Accrued interest	843	
Short-term investments (Note #3)	<u>503,008</u>	
TOTAL ASSETS		<u>8,855,487</u>
LIABILITIES		
Research grants payable - current portion (Note #4)	3,385,461	
Research grants payable - long-term portion (Note #4)	<u>200,280</u>	
TOTAL LIABILITIES		<u>3,585,741</u>
NET ASSETS		
Unrestricted net assets	<u>5,269,746</u>	
TOTAL NET ASSETS		<u>5,269,746</u>
TOTAL LIABILITIES & NET ASSETS		<u>8,855,487</u>

The notes to the financial statements are an integral part of these statements.

STATEMENT OF ACTIVITIES

REVENUE & GAINS		
Contributions	4,298,813	
Net Interest Income (Note #3)	11,659	
Unrealized Gain on Investments (Note #3)	<u>9,525</u>	
TOTAL REVENUE & GAINS		<u>4,319,997</u>
EXPENSES		
Program Services		
Research Grants	6,096,444	
Patient Expense	20,000	
ALS Meeting Grants	15,000	
Peer Review of Research Grants	35,000	
Supporting Services		
Management and general	17,569	
Fundraising	<u>281,790</u>	
TOTAL EXPENSES		<u>6,465,803</u>
CHANGES IN NET ASSETS		<u>(2,145,806)</u>
NET ASSETS AT BEGINNING OF YEAR (as previously stated)	9,726,367	
Less: Prior Period Adjustment (Note #7)	<u>(2,310,815)</u>	
NET ASSETS AT BEGINNING OF YEAR - RESTATED		<u>7,415,552</u>
NET ASSETS AT END OF YEAR		<u>5,269,746</u>

The notes to the financial statements are an integral part of these statements.

CASH FLOWS

CASH RECEIPTS FROM OPERATING ACTIVITIES	
Contributions	4,171,305
Interest Income	<u>77,178</u>
TOTAL CASH RECEIPTS FROM OPERATING ACTIVITIES	<u>4,248,483</u>
CASH DISBURSEMENTS FROM OPERATING ACTIVITIES	
ALS Meetings	15,000
Bank Charges	80
Contract Project Management / Fundraising	144,406
Fundraising	44,877
Legal & Accounting	8,000
Licensing Fees	3,238
Insurance	2,868
Office Supplies	2,383
Patient Expense	20,000
Research Grants	5,306,150
Taxes - MA	<u>1,000</u>
TOTAL CASH DISBURSEMENTS FROM OPERATING ACTIVITIES	<u>5,548,002</u>
NET CASH RECEIVED FROM OPERATING ACTIVITIES	<u>(1,299,519)</u>
CASH FROM INVESTING ACTIVITIES	
Sale of investments	<u>4,150,000</u>
NET CASH RECEIVED FROM INVESTING ACTIVITIES	<u>4,150,000</u>
TOTAL INCREASE IN CASH & CASH EQUIVALENTS	<u>2,850,481</u>
CASH & CASH EQUIVALENTS - BEGINNING OF YEAR	<u>5,501,156</u>
CASH & CASH EQUIVALENTS - END OF YEAR	<u>8,351,637</u>
NON-CASH ITEMS	
Donated fund-raising expenses	92,508
Donated professional services	35,000

The notes to the financial statements are an integral part of these statements.

NOTES TO FINANCIAL STATEMENTS AS OF DECEMBER 31, 2010

ALS Therapy Alliance, Inc. (the Organization) is a not-for-profit corporation organized to raise funds from individual donors to fund ALS (Amyotrophic Lateral Sclerosis) research. The organization provides a vehicle for a diverse group of scientists and clinicians to coordinate research related to ALS. Applications for research grants solicited from research hospitals and other organizations are reviewed by the board of directors and selected for funding. Those projects funded are required to present their findings to the Organization. The Organization is supported primarily through donor contributions from a three week joint fundraising campaign with CVS Caremark, Inc. Approximately 95% of the Organization's support for the current and prior years came from the CVS Caremark, Inc. joint fundraising campaign.

NOTE 1: SIGNIFICANT ACCOUNTING POLICIES:

- The Organization is exempt from taxation under section 501(c)(3) of the Internal Revenue Code and is classified as other than a private foundation.

- B. Method of accounting: The Organization uses the accrual method of accounting for financial and tax reporting. Calendar year reporting has been adopted.
- C. Contributions: Contributed services requiring specific expertise are recorded at the estimated fair value of the contribution. The value of contributed services not requiring specific expertise and contributed shared office space are not recorded as they are immaterial in value. Since its inception a significant portion of the Organization's fund-raising expenses have been donated by an unrelated organization. The Organization recognizes income to the extent of the actual cost of these donated expenses and services, as well as an expense for the corresponding amount.
- D. Investments: Investments in US Treasury Securities are reported at their fair values in the statement financial position. Unrealized gains and losses are included in the change in net assets.
- E. Cash and Cash Equivalents: For the purposes of the statement of cash flows, the Organization considers all short-term U.S. Treasury securities with an original maturity of three months or less to be cash equivalents.
- F. Use of estimates: The preparation of financial statements using generally accepted accounting principles requires management to make estimates and assumptions that affect certain reported amounts and disclosures. Accordingly, actual results could differ from those estimates.
- G. Property and Equipment: The Organization capitalizes property and equipment over \$1,000. Lesser amounts are expensed. Purchase property and equipment is capitalized at cost. Donations of property and equipment are recorded as contributions at their estimated fair value and reported as unrestricted contributions unless the donor has restricted the asset for a specific purpose. As of the date of these financial statements, the Organization owned no property and equipment.

NOTE 2: EXCESS DEPOSITS:

The Organization had deposits with banks and brokerages on December 31, 2010 that exceeded the FDIC and SIPC limits by \$2,195,242 and \$4,875,890 respectively.

NOTE 3: INVESTMENTS:

The Organization held short-term investments in U. S. Treasury notes totaling \$503,008 that mature within one year. These investments are reported at fair value determined by using quoted prices in active markets for identical assets (Level 1 input) at the close of the business day. Temporary fluctuations in fair value are reported as unrealized gains and losses. Substantially all securities are held to their maturity, resulting in no realized gain or loss.

The following schedule summarizes the investment return and its classification in the statement of activities for the year ended December 31, 2010:

	Unrestricted
Interest income	\$ 61,760
Less: Amortized bond premium paid	(50,101)
Net interest income	11,659
Net unrealized gain	<u>9,525</u>
Total investment return	<u>\$ 21,184</u>

NOTE 4: RESEARCH GRANTS PAYABLE:

As of December 31, 2010, the Organization had research grant commitments for single and multi-year projects in the amount of \$3,585,741. All research grant contracts require the researchers to provide the Organization with annual progress reports and an accounting of expenditures. Multi-year projects require this reporting prior to disbursement of subsequent year funding. As of the date of these financial statements, research grant commitments total \$3,385,461 for 2011 and \$200,280 for 2012.

NOTE 5: CONTRIBUTED SERVICES:

Seven members of the Board of Directors provide highly advanced scientific expertise required to review research proposals. Based upon estimated 25 hours required to peer review proposals and attend board meetings, the Organization reported the estimated value of these scientific services at \$35,000 as both contribution revenue and program service expense.

In 2010 an unrelated organization paid \$92,508 for promotional fundraising materials. The actual cost of the fundraising materials is reported as contributions revenue and fundraising expense.

NOTE 6: RELATED PARTY TRANSACTIONS:

Seven of the board members of the Organization are highly trained research scientists with expertise in the area of ALS research. As scientists, some have submitted research grant applications following the Summary of Guidelines for Application requirements as approved by the board. When a grant proposal submitted by a board member is reviewed by the board, that board member is not allowed to vote or remain in the room when such proposal is discussed and voted upon. During the year ended December 31, 2010, \$2,051,083 of board member research projects were approved, \$1,463,575 were funded and the remaining \$587,508 is reported as research grants payable.

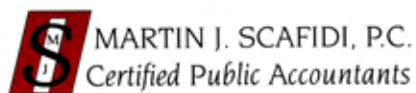
NOTE 7: PRIOR PERIOD ADJUSTMENT:

Several research projects approved in 2009 remained unfunded at the end of that calendar year and were not reported on the financial statements as research grants payable for that year. Research grants payable on December 31, 2009 were previously reported as \$484,632 and should have been reported as \$2,795,447 resulting in an increase in research grant expense and decrease in unrestricted net assets for the prior year of \$2,310,815.

NOTE 8: SUBSEQUENT EVENTS:

The Organization has evaluated subsequent events through February 22, 2011, the date which the financial statements were issued.

2011 Independent Auditor's Report



Board of Trustees
ALS Therapy Alliance, Inc.
Needham, Massachusetts

We have audited the accompanying statement of financial position of the ALS Therapy Alliance, Inc. (A Non-Profit Corporation) ("the Organization") as of December 31, 2011 and the related statements of activities and changes in net assets, functional expenses, and cash flows for the year then ended. These financial statements are the responsibility of the Organization's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with auditing standards generally accepted in the United States of America. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of the ALS Therapy Alliance, Inc. as of December 31, 2011 and the results of its activities and cash flows for the year then ended in conformity with accounting principles generally accepted in the United States of America.

Martin J. Scafidi, P.C.
Peabody, Mass.
June 15, 2012

Financials 2011

FINANCIAL POSITION

	<u>Assets</u>
Current Assets:	
Cash and cash equivalents	\$ 9,612,077
Prepaid expenses	1,094
Total current assets	<u>9,613,171</u>
Total assets	<u>\$ 9,613,171</u>
	<u>Liabilities and Net Assets</u>
Current Liabilities:	
Accrued expenses	\$ 8,583
Research grants payable - current	1,922,393
Total current liabilities	<u>1,930,976</u>
Net Assets:	
Unrestricted net assets	<u>7,682,195</u>
Total net assets	<u>7,682,195</u>
Total liabilities and net assets	<u>\$ 9,613,171</u>

CASH FLOWS

Cash Flows From Operating Activities:	
Increase in unrestricted net assets	\$ 2,412,449
Adjustment to reconciled change in unrestricted net assets to cash flow from operations:	
Changes in:	
Accrued interest	843
Prepaid expenses	(1,094)
Accrued expenses	8,583
Research grants payable	(1,663,348)
Total adjustments	<u>(1,655,016)</u>
Net cash provided by operating activities	<u>757,433</u>
Cash Flows From Investing Activities:	
Redemptions of marketable securities	<u>503,008</u>
Net cash provided by financing activities	<u>503,008</u>
Change in Cash and Cash Equivalents	<u>1,260,441</u>
Cash and Cash Equivalents, Beginning of Year	<u>8,351,636</u>
Cash and Cash Equivalents, End of Year	<u>\$ 9,612,077</u>

ACTIVITIES AND CHANGES IN NET ASSETS

Unrestricted Net Assets	
Revenues:	
Contributions	\$ 4,502,241
Special events, net of costs of \$18,669	21,915
Interest	2,248
Total unrestricted revenues	<u>4,526,404</u>
Expenses:	
Program services:	
Research grants	1,620,557
Program administration	20,100
ALS meeting grants	54,662
Research grant peer review	35,000
Total program services expense	<u>1,730,319</u>
Supporting services:	
Management and general expenses	44,691
Fundraising	338,945
Total unrestricted expenses	<u>2,113,955</u>
Increase in Unrestricted Net Assets	<u>2,412,449</u>
Unrestricted Net Assets, Beginning of Period	<u>5,269,746</u>
Unrestricted Net Assets, End of Period	<u>\$ 7,682,195</u>

FUNCTIONAL EXPENSES

	<u>Program Services</u>	<u>Management and General</u>	<u>Fund Raising</u>	<u>Total</u>
Accounting	\$ -	\$ 4,388	\$ -	\$ 4,388
Fundraising campaign advertising and publicity	-	-	62,353	62,353
Fundraising campaign awards	-	-	39,720	39,720
License fees	-	-	25,000	25,000
Insurance	-	1,823	-	1,823
Management agent	20,100	30,150	50,250	100,500
Meetings and conferences	54,662	80	22,298	77,040
Office supplies/expenses	-	3,046	-	3,046
Outside consultants	-	-	99,026	99,026
Peer review expense	35,000	-	-	35,000
Postage and mailings	-	-	28,378	28,378
Printing and copying	-	-	11,920	11,920
Research grants	1,620,557	-	-	1,620,557
Telephone	-	780	-	780
Website development and maintenance	-	4,424	-	4,424
	<u>\$ 1,730,319</u>	<u>\$ 44,691</u>	<u>\$ 338,945</u>	<u>\$ 2,113,955</u>

Financials 2011

CASH FLOWS

	<u>12/31/2011</u>	<u>12/31/2010</u>	<u>Change</u>	<u>Operating</u>	<u>Financing</u>	<u>Investing</u>
Cash	9,612,077	8,351,636	1,260,441			
Accrued interest	-	843	(843)	843		
Investment in marketable securities	-	503,008	(503,008)			503,008
Prepaid expenses	1,094	-	1,094	(1,094)		
Accrued expenses	(8,583)	-	(8,583)	8,583		
Grants payable	(1,922,393)	(3,585,741)	1,663,348	(1,663,348)		
Unrestricted net assets	(7,682,195)	(5,269,746)	(2,412,449)	2,412,449		
	<u>-</u>	<u>-</u>	<u>-</u>	<u>757,433</u>	<u>-</u>	<u>503,008</u>

NOTES TO FINANCIAL STATEMENTS AS OF DECEMBER 31, 2011

NOTE 1: ORGANIZATION AND PURPOSE

ALS Therapy Alliance, Inc. ("the Organization") is a private, not-for-profit organization incorporated in Massachusetts in 2002. Its purpose is to raise funds from individual donors to fund research into Amyotrophic Lateral Sclerosis ("ALS"). The Organization provides a vehicle for a diverse group of scientists and clinicians to coordinate research related to ALS. Applications for research grants are solicited from research hospitals and other organization, are reviewed by the board of directors, and selected for funding. Those projects the Organization funds are required to present their findings to the Organization. The Organization's primary source of funds is donor contributions collected during a three week joint fundraising campaign with CVS/Caremark, Inc. conducted throughout the United States of America. During the fundraising campaign, individuals donate cash by depositing it in containers in CVS/Caremark, Inc. stores. CVS/Caremark, Inc. collects and subsequently remits the funds to the Organization. Approximately 95% of the Organization's support for the current and prior years came from the CVS/Caremark, Inc. joint fundraising campaign.

NOTE 2: SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Accounting

The Organization recognizes revenues and expenses according to the accrual basis of accounting. Accordingly, it recognizes revenues when earned and expenses when incurred.

Financial Reporting and Net Assets

The Organization's financial statements report information regarding its financial position and activities according to the following three classes of net assets:

- Unrestricted net assets: resources received by the Organization for use at the discretion of its management and Board of Directors in carrying out its programs.
- Temporarily restricted net assets: resources received by the Organization with donor imposed restrictions that limit their use to a specific purpose or period of time. When the purpose or time restrictions are met, temporarily restricted net assets are reclassified to unrestricted net assets and are reported in the statements of activities as net assets released from restrictions.
- Permanently restricted net assets: resources received by the Organi-

zation with donor-imposed restrictions that require the Organization to maintain the funds permanently in accordance with the donor's specified purpose. Generally, the donors will allow the Organization use of income earned on these funds as unrestricted or temporarily restricted net assets.

The Organization had no temporarily or permanently restricted net assets as of December 31, 2011.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America requires management to make estimates and assumptions that affect certain reported amounts and disclosures. Accordingly, actual results could differ from these estimates.

Subsequent Events

In preparing these financial statements, the Company has evaluated events and transactions for potential recognition or disclosure through June 15, 2012, the date the financial statements were available to be issued.

Cash and Cash Equivalents

The Organization considers all cash, money market accounts, and highly liquid certificates of deposits and short-term investments with an original maturity within three months of purchase to be cash and cash equivalents.

Investments in Marketable Securities

Investments in marketable securities are reported at their fair values in the statement of financial position. Unrealized gains and losses are included in the statement of changes in net assets. The Organization held no marketable securities at December 31, 2011. The Organization redeemed U.S. Treasury securities, which were included in investments in marketable securities, during the year ended December 31, 2011.

Fixed Assets and Depreciation

The Organization policy is to capitalize property and equipment at cost if purchased or fair market value if donated if the equipment's value is greater than \$1,000. It records depreciation on its fixed assets using the straight-line method over their estimated useful life. The Organization records expenditures for maintenance, repairs, and betterments that do

not materially prolong the normal useful life or expand the capacity of the asset as expenses when incurred. The Organization owned no property and equipment as of December 31, 2011.

Financial Instruments

The carrying value of cash and cash equivalents, grants payable, and accrued expenses approximate fair value because of the terms and the relatively short maturity of these financial instruments.

Revenue Recognition

The Organization records its revenues from donations as unrestricted, temporarily restricted, or permanently restricted support, depending of the existence or nature of any donor stipulations that limit the use, as to purpose or time, of the donated assets. All of the Organizations donations, income from special events (golf tournament) and interest are considered unrestricted income.

Donations are recognized as revenue when received. Special events revenues are recognized as revenue when the event occurs.

Functional Allocation of Expenses

The Organization has summarized the costs of providing its program and activities on a functional basis in the statement of activities. The Organization allocates certain costs between program services and supporting services based upon the nature of the cost, the benefit to the Organization, and management's estimate of the percentage attributable to each function.

Advertising Costs

The Company records advertising costs as incurred. Total advertising expense for the year ended December 31, 2011 was \$65,353 and is included in the financial statements as advertising and publicity expense.

NOTE 3. FEDERAL INCOME TAXES

The Organization qualifies as a tax-exempt organization other than a private foundation under Section 501 (c) 3 of the Internal Revenue code. Accordingly, no provision for federal income tax is required.

The Organization is subject to routine audits by taxing jurisdictions; however, there are currently no audits for any tax periods in progress. The Organization believes it is no longer subject to income tax examinations for years prior to 2009.

NOTE 4. RESEARCH GRANTS PAYABLE

Subsequent to year-end, the Organization awarded additional research grants had research grant commitments (see Note 6) for various projects totaling \$2,656,397, which are payable under the terms of the individual grants in the years ending December 31,

2012	\$ 1,271,020
2013	1,149,377
2014	236,009

NOTE 5. CONTRIBUTED SERVICES

Seven of the members of the Board of Directors are highly trained doctors or research scientists who provide the highly advanced scientific knowledge and expertise required to peer review all of the proposals for research grants and the subsequent reporting of the results. During the year ending December 31, 2011, the Organization reported the estimated value of those specialized scientific peer review services as contributions and programs service expenses in the amount of \$35,000, respectively. The Organization's valuation is based on an estimated 10 hours per member in performing the peer review services that would otherwise have been contracted for.

NOTE 6. RELATED PARTY TRANSACTIONS

The Organization's board of directors includes several highly trained research scientists with expertise in the area of ALS research. As scientists, some have applied for research grants following the Summary of Guidelines for Application requirements that has been approved by the Board. When a board member submits a grant proposal, that board member is not allowed to be in the room when the grant proposal is review and discussed by the remaining board members and is not allowed to vote upon the proposal.

During the year ended December 31, 2011, research grants from board members totaling \$450,000 were approved, \$886,631 were funded, and \$402,952 were included in research grants payable (see Note 4.).

NOTE 7. MANAGEMENT AGREEMENT

The Organization has a one year agreement with a management agent ("the Agent") who performs various day-to-day administrative, fiscal, human resources, and fundraising coordination activities on behalf of the Organization. The Agent receives management fees for services provided payable in monthly installments of \$8,538 through October 2012. The Agent is also reimbursed for various out-of-pocket expenses incurred in providing the management services. Total fees and expenses paid to the Agent during the year ended December 31, 2012 was \$132,997.

NOTE 8. CONCENTRATION OF CREDIT RISK

Financial instruments subjecting the Organization to concentrations of credit risk include cash.

The Organization maintains its cash in bank and money market mutual organization accounts that, at times, exceeds the \$250,000 limit of deposit insurance provided by the Federal Deposit Insurance Corporation. The Organization has not experienced any losses in these accounts and does not believe it is subject to any material credit risk from these accounts.

NOTE 9. CASH FLOW INFORMATION

For the year ending December 31, 2011, the Organization made no cash payments for interest or income taxes.

Grant Summaries

PROJECT: MicroRNA Profiles in ALS

Investigator: Victor Ambros, Ph.D.

Program in Molecular Medicine, University of Massachusetts Medical School, United States

Co-Investigators: Alexey Wolfson, Ph.D., Catherine Sterling, Ph.D., & Rosalind Lee (Senior Research Associate)

Extracellular microRNAs are detected circulating in normal human blood plasma and cerebrospinal fluid (CSF). Circulating microRNAs are easily assayed by QRT/PCR or deep sequencing and provide potentially powerful reporters of the physiological state of their cells of origin. Accordingly, we have used quantitative RT/PCR to determine the levels of all known human microRNAs in samples of CSF from normal subjects and patients with ALS.

Our preliminary findings indicate that more than 100 microRNAs are robustly detected in human CSF, and that there seem to be a set of specific microRNAs whose expression profile in CSF may serve as an indicator of ALS. These preliminary data, as well as others implicating miRNA in homeostasis of neurons, support the view that microRNAs in the central nervous system may be involved in neurodegenerative disorders such as motor neuron disease.

We have therefore started a series of studies to characterize the identities and quantities of microRNAs in various CNS compartments, particularly cerebrospinal fluid, with the goal of developing miRNA profiles of both normal and neurodegenerative CSF. Our goals are to characterize the natural systemic transport of small RNAs in the CNS and to evaluate circulating microRNAs as biomarkers in ALS.

PROJECT: A Multi-center Study for the Discovery and Validation of ALS Biomarkers

Investigator: James D. Berry, M.D., M.P.H.

Neurology Clinical Trials Unit, Massachusetts General Hospital, United States

Co-Investigators: Merit E. Cudkowicz, M.D., M.Sc., Robert P. Bowser, Ph.D., Shafeeq Ladha, M.D., Kevin B. Boylan, M.D., Robert H. Brown, Jr., D.Phil., Jonny Salameh, M.D., Robert Ferrante, Ph.D., M.S., Jonathan D. Glass, M.D., David Lacomis, M.D., & Gerry Shaw, Ph.D.

There is an ongoing effort to discover biomarkers of amyotrophic lateral sclerosis (ALS) in blood and cerebrospinal fluid (CSF). Current approaches use cross-sectional analyses, comparing samples from ALS patients to those from healthy volunteers and/or disease controls.

The present study is designed to create a repository of plasma and CSF collected from patients with ALS every four months for at least two years. Rigorous standard operating procedures have been developed to standardize the collection, processing and storage of biofluids, thus reducing preanalytic sample variability. At each visit, extensive clinical information is also collected, including clinical ALS outcome

measures such as the ALSFRS-R, vital capacity, Ashworth Spasticity Scale, Hand-Held Dynamometry, and a screening exam for frontotemporal dementia. Once this biorepository and the linked clinical information database have been established, they will be used to explore novel biomarkers of ALS diagnosis and progression in four predefined projects being conducted at the Barrow Neurologic Institute, Emory University, the Mayo Clinic Florida and the University of Massachusetts. These projects will employ unbiased and targeted proteomics, antibody-capture protein identification and RNA isolation techniques to investigate novel biomarkers and attempt to validate previously reported candidate biomarkers. Project coordination and data management is performed through the fifth collaborative center, Massachusetts General Hospital.

At the end of the study, these longitudinally collected samples will become a part of the Northeast ALS Consortium biorepository, where they will be shared with other ALS biomarker researchers. Such a resource does not currently exist in the field of ALS and will be a valuable addition.

PROJECT: Investigating a gain of Toxic Function of ALS-linked Mutant FUS/TLS in the Squid Axoplasm Model of Axonal Transport

Investigator: Daryl A. Bosco, Ph.D.
Department of Neurology, University of Massachusetts Medical Center, United States

Co-Investigators: Scott Brady, Ph.D., Gerardo Morfini, Ph.D., & Reddy Ranjith K. Sama (Graduate Student)

The focus of our studies is to test the hypothesis that mutant-FUS proteins exert a gain of toxic function that is linked to ALS pathogenesis. Mutations in FUS have been linked to both familial and sporadic forms of ALS. Most ALS-linked mutations in FUS cause the protein to mislocalize from the nucleus to the cytoplasm. Using the squid axoplasm assay for fast axonal transport, we found that mutant-FUS inhibits transport in both the retrograde and anterograde directions.

Therefore, mutant-FUS proteins impair axonal transport. In contrast, the normal wild-type FUS protein has no effect on transport in this assay. By employing pharmacological inhibitors against cellular kinases, we found that the effect of mutant FUS on transport is modulated by p38 MAPK, a kinase that is normally activated in response to stress. These data raise the possibility

that when mutant-FUS mislocalizes to the cytoplasm, it triggers p38 MAPK activation, which in turn impairs axonal transport. Interestingly, our previous studies revealed that mutant- and aberrantly modified forms of SOD1, another ALS-associated protein, also impair axonal transport through a mechanism that involves p38 MAPK activation. Motor neurons that are degenerated in ALS may be particularly susceptible to defects in axonal transport by virtue of their long axons, which can extend up to one meter in length. We are beginning to recapitulate the effect of mutant-FUS on p38 MAPK activation in mammalian cell culture models.

PROJECT: Identification of FUS/TLS & TDP-43 Transcriptional Targets

Investigator: Miriam Bucheli, Ph.D.
San Francisco University of Quito, Ecuador

Co-Investigators: Daniel Day (Graduate Student), Mazhar Adli (Postdoc), Monica Carrasco (Postdoc), Lulu Tsao (Undergraduate Student), Peter Park (Professor) & Tom Maniatis, Ph.D.

Our first objective was to characterize the transcription/RNA processing activities of FUS/TLS and TDP-43 through the identification of their gene targets. There is no knowledge of all the genomic targets that are shared between FUS/TLS and TDP-43. Based on the probability of overlap for similar transcriptional events at some sites, our second objective was to identify those genes that share occupancy by FUS/TLS and TDP-43 as potential sites of misregulation in ALS and to follow up with their characterization.

Results: TDP-43 was first identified as the major protein in cytoplasmic inclusions found in neurons and glia of individuals with sporadic and some familial forms of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). The genetic association of TDP-43 with ALS is a more recent discovery, with dominant mutations in TARDBP (TDP-43 gene) first identified in several ALS families and later in sporadic cases. The RNA binding protein TDP-43 is a ubiquitously expressed protein that binds and regulates the expression of transcripts important for neuronal development. While most transcripts bound by TDP-43 are nuclear, it is not clear whether binding occurs co-transcriptionally. To answer this question, chromatin immunoprecipitation followed by next-generation sequencing was used to understand the genomic patterns of binding for the normal and mutant M337V TDP-43 in motor neurons (MNs). The MNs were derived from induced pluripotent stem (iPS) cells generated from an ALS patient and a control individual. Our results suggest that the mutant M337V

Grant Summaries

acquires properties distinct from that of the normal TDP-43. The effect of the imperfect binding of the mutant protein on gene expression was assessed in the context of epigenetic modifications that function as signals for the activation (histone 3 lysine-36 tri-methylation) or repression (histone 3 lysine-27 tri-methylation) of genes. Our results reveal how a mutation in the protein may induce subtle alterations in its occupancy of some genes and directly or indirectly lead to changes in the expression of genes involved in neuronal development.

PROJECT: The role of Sarm in Axon Degeneration and ALS

Investigator: Marc Freeman, Ph.D.

Department of Neurobiology/HHMI, University of Massachusetts Medical School, United States

Co-Investigators: Jeannette Osterloh (Ph.D. track student) & Timothy Rooney (M.D./Ph.D. track student)

Axon degeneration is a common feature of peripheral neuropathy and neurodegenerative diseases, including ALS. Axonal and synaptic degradation ultimately leads to loss of functional integrity of affected neural circuits and disease progression. Surprisingly little is known about molecular pathways mediating axonal self-destruction in any context. Wallerian degeneration is a very useful model to study axonal degeneration after injury and is mechanistically related to axon destruction in disease, but is fundamentally different from apoptotic cell death. Using *Drosophila* forward genetics we found that loss of dSarm (*Drosophila* sterile Armadillo/Toll-Interleukin receptor homology domain protein) blocked the degeneration of severed axons and their synapses for the lifespan of the fly. dSarm is an ancient member of the TIR domain-containing family of proteins which are well-conserved from *C. elegans* to humans.

Strikingly, we have found that mouse *sarm*^{-/-} knockout animals also exhibit profound protection of axon after injury: severed axons remain intact after sciatic nerve lesion for over two weeks *in vivo*, and DRG and cortical neurons are strongly protected after axotomy *in vitro*. Thus dSarm/SARM is a founding member of a novel and conserved axon death signaling pathway.

Our work shows that loss of function mutations in specific genes can completely suppress axon degeneration and defines it as a programmed process of auto-destruction. Functional blockade of the human SARM1 signaling pathway now becomes an exciting new therapeutic approach to suppress axonal and synaptic loss in neurodegenerative diseases. We are therefore now exploring

whether *sarm* mutants can suppress mouse models of ALS (SOD-G93A).

PROJECT: Generation and Characterization of Induced Pluripotent Stem Cell Lines Containing Defined Genetic Mutations Implicated in ALS

Investigator: Fen-Biao Gao, Ph.D.

University of Massachusetts Medical School, United States

Co-Investigators: Sandra Almeida, Ph.D., & Zhijun Zhang, Ph.D.

How genetic and environmental factors contribute to the pathogenesis of ALS remains poorly understood. Mutations identified in familial ALS cases have been very informative and helped us to dissect the molecular and cellular pathways that are misregulated in ALS. Since the groundbreaking identification of SOD1 mutations in ALS, several new ALS genes have been reported, including TDP-43, FUS and C9orf72. These recent advances raise the possibility that misregulation of RNAs is a major mechanism of ALS pathogenesis.

Despite recent breathtaking advancements in human genetics studies, our understanding of ALS pathogenesis at the molecular and cellular levels is still critically lacking, which significantly hinders efforts to find a cure. Animal models have been useful but many scientific findings in animal models fail to translate into feasible therapies in humans, in part because of species differences in physiology and toxicology. Moreover, assays with human neurons may be one of the best ways to screen drugs for therapeutic interventions.

One way to generate disease-specific human neurons is to create induced pluripotent stem (iPS) cells from human fibroblasts. These iPS cells are genetically identical to the patient and will therefore carry the same disease mutation. Thus, they afford an excellent opportunity to investigate disease mechanisms, screen for drugs, and develop individualized medicines. With the support of ATA and other agencies, we have generated ALS patient-specific iPS cells containing specific genetic mutations. We are continuing to use the iPS cell models to further dissect the molecular pathways misregulated in ALS.

PROJECT: Mechanisms of Mutant FUS-mediated Motor Neuron Disease

Investigator: Lawrence J. Hayward, M.D., Ph.D.
University of Massachusetts Medical School, United States

Co-Investigators: Hae Kyung Ko (Ph.D. Candidate) & Hongru Zhou (Research Assistant)

Mutations in FUS, a nucleic acid binding protein involved in gene transcription and RNA processing, cause ~5% of familial ALS cases. The Hayward lab is establishing cellular and animal models to understand how mutant FUS perturbs cellular homeostasis in vivo so that we may identify new targets for ALS therapy. FUS is a multifunctional protein, and possible insults within compartments of the motor neuron (e.g., in the nucleus, soma, dendrites, axons or terminals) or within supporting cell types in the spinal cord also remain undefined. To address important mechanistic questions and to complement transgenic mouse modeling approaches already in progress, we are studying the consequences of mutant FUS in cell cultures and in experimentally accessible zebrafish models of ALS. We are constructing vectors for transgenic expression of normal or ALS mutant FUS and for targeted perturbation of the endogenous zebrafish FUS gene. These models will be analyzed to detect ALS-like abnormalities to discern whether the FUS mutations trigger dominant gain-of-function, loss-of-function or dominant-negative mechanism(s) affecting motor neurons. Moreover, these models may allow us to design one or more assays to screen for small molecule or genetic suppressors of the observed phenotypes.

PROJECT: Proposal to Leonard Tow for National ALS Mouse Model Repository

Investigators: Michael Hyde, M.Ed., & Cathleen Lutz, Ph.D.
Jackson Laboratory, United States

Research in ALS mouse models has focused primarily on mutations in the SOD1 gene. Now, recent discoveries point to defects in RNA processing proteins as a key to understanding the causes of the disease. Further, mutations in the TARDBP gene have been shown to cause familial ALS in a small proportion of cases. Similar experiments uncovered mutations in a related RNA processing gene called fused in sarcoma (FUS). These discoveries offer new hope for therapeutic intervention. Creation and rapid distribution of mouse models of these disorders is crucial to finding treatments. Unfortunately, many scientists are slow to make new mouse models available, while high costs and complex licensing requirements further block the flow of mice to ALS researchers.

To alleviate this problem, the Jackson Laboratory requests \$630,755 over three years to establish the National ALS Mouse Model Repository at the Jackson Laboratory. The goals of this repository will be to: 1) actively acquire current ALS models; 2) standardize their genetic background; 3) provide genetic and phenotypic quality assurance around the new models; 4) establish embryonic stem (ES) cells for models that prove the most useful; and 5) quickly make these resources available to the scientific community. This project secured the approval of the ALS Association (ALSA) and a number of top ALS investigators from around the world, including Columbia University's Dr. Tom Maniatis, during an October 2009 meeting convened to assess interest in establishing an ALS mouse repository at the Jackson Laboratory.

PROJECT: ALS Mouse Trial

Investigator: Robert Molinari, Ph.D., M.B.A.
Retrotepe, United States

Oxidative damage initiated by ROS is a major contributor to the functional decline that is characteristic of age-related diseases, including CNS disease. Reactive carbonyls such as HNE, ONE and HHE formed from both omega-3 and omega-6 PUFA oxidation by ROS have been shown to play a role in the etiology of ALS. Modifications of PUFAs in diet are known to play a positive role in reducing the risk of developing ALS and are therefore known to be an effective intervention.

We propose that "reinforcing" essential PUFAs with isotopic replacement via dietary intake will reduce lipid peroxidation and decelerate HNE-mediated toxic cascades that contribute to neuronal degeneration in ALS. We aim to stabilize PUFAs by substituting D (deuterium, the naturally occurring, heavy isotope variant of hydrogen) for H at oxidation-prone bis-allylic sites of these essential fatty acids. Because the D-C bond is more stable due to the isotope effect, this substitution significantly reinforces the C-H bond that is first broken in lipid peroxidation, without changing the chemical identity of PUFAs. A decrease in the formation of intracellular toxic lipid peroxides reduces the amount of reactive carbonyls and diminishes the activation of toxic cellular cascades. We have successfully tested this approach in yeast and PD mouse model. In this proposed study, we will test whether our novel molecular stabilization approach reduces cellular oxidative damage in the ALS SOD1 G93A mouse model.



PROJECT: Mechanisms underlying MAPK Activation and Axonal Transport Deficits in Familial ALS

Investigator: Gerardo Morfini, Ph.D.
Department of Anatomy and Cell Biology, University of Illinois at Chicago, United States

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder involving progressive loss of function and dying-back degeneration of motor neurons. Most ALS cases are sporadic (sALS), but familial forms (fALS) result from mutations in the enzyme superoxide dismutase 1 (SOD1) and other unrelated genes. The phenotypic similarities between sALS and fALS suggest the existence of common pathogenic mechanisms, but a molecular basis for these mechanisms remains elusive.

The marked vulnerability of motor neurons observed in ALS contrast sharply with the ubiquitous tissue expression of SOD1, suggesting that alterations in cellular processes particularly critical for the function and survival of these neurons play a central role in ALS pathogenesis. The enormous size and complex cellular architecture of motor neurons cells renders these cells uniquely vulnerable to alterations in intracellular signaling and axonal transport (AT) mechanisms. Accordingly, abnormal activation of protein kinases and reductions in AT represent well-documented ALS hallmarks, but relationships between these pathogenic events remained unknown.

Grant Summaries

Our recent studies indicate that pathogenic SOD1 polypeptides inhibit kinesin-1 based AT by a mechanism involving activation of the kinase p38 and upstream mitogen-activated protein kinases (MAPKs). Using cellular and animal models of SOD1-related fALS, experiments under ATA funding currently evaluate alterations in AT of specific kinesin-1 isoforms and their transported membrane cargoes. Additionally, pharmacological, biochemical and cell biological approaches are being used to identify specific MAPKs mediating the increase in p38 activity induced by pathogenic SOD1. Results from these experiments will help identify novel therapeutic targets in ALS.

PROJECT: The Pooled Resource Open Access Clinical Trials (PO-ACT) Database

Investigator: Prize4Life & NEALS, United States

There have been multiple large Phase II and Phase III ALS clinical trials conducted over the past 15 years. While the vast majority of these trials, with the exception of the Riluzole trials, have not resulted in the identification of new therapies for ALS, there is still great value in the patient data collected during the course of these studies. Despite their wealth of information, clinical trial datasets have not historically been made readily available to the ALS research community and comparisons across datasets are extremely difficult.

Pooling data from existing public and private sources of trial data may yield a database of thousands of ALS patient records, which will be far larger than any single trial or existing dataset. Such a set of pooled data would not only yield useful information about many aspects of the conduct of ALS clinical trials, but could also be “data-mined” for unique observations, novel correlations, patterns of disease progress, epidemiological data and a variety of still unconsidered analyses.

With the support of the ATA, PRO-ACT Database project will design and build an ALS clinical trial database with merged datasets and an underlying searchable data platform. The PRO-ACT Database will be freely available, exclusively for research purposes, to members of the research and development (R&D) community (industry, government and academe), which will provide the ALS research community with an invaluable resource in the effort to develop treatments and a cure.

PROJECT: Characterizing the Surface Hydrophobicity of ALS Mutants of SOD1 by Novel Fluorescent Probes

Investigator: Ashutosh Tiwari, Ph.D.
Department of Chemistry, Michigan Technological University,
United States

Co-Investigators: Shilei Zhu, Ph.D. (Postdoc), Nethaniah Dorh (Graduate Student) & Claire Drom (Undergraduate Researcher)

In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), prion diseases and Huntington's disease (HD), where protein misfolding is implicated, intracellular or extracellular aggregates are observed at the end stage of the disease. The proteins involved in these diseases are expected to adopt non-native conformations due to mutation or stress and the exposed hydrophobic surfaces can result in aberrant interactions with themselves or other cellular constituents. Although hydrophobic fluorophore such as 1-anilinonaphthalene-8-sulfonic acid (ANS) has been widely used as a probe for hydrophobic exposure of proteins, it provides only a global measure of hydrophobicity. Furthermore, effective probes for identifying specific amino acids that are aberrantly exposed on protein surfaces due to mutation or misfolding are lacking. We propose to synthesize novel water soluble, neutral, hydrophobic fluorescent probes with high quantum yield having reactive functional groups that can covalently bind to the side chain of amino acids in the vicinity of the exposed hydrophobic region. Using these novel compounds, we will characterize the aberrantly exposed hydrophobic surface of mutant Cu/Zn Superoxide Dismutase (SOD1) associated with ALS.

PROJECT: Research Conference of International Consortium on Superoxide Dismutase and ALS

Investigators: Lawrence Hayward, M.D., Ph.D., & Daryl Bosco, Ph.D.
University of Massachusetts Medical School, United States

The 9th Research Conference of the International Consortium on Superoxide Dismutase and ALS (ICOSA) was held at the University of Massachusetts Medical School on May 20-22, 2010. The meeting was organized by Dr. Lawrence Hayward and Dr. Daryl Bosco and included 70 participants from UMass Medical School, Brandeis University, the University of California at Los Angeles, the University of Texas, the University of Liverpool (UK), Umeå

University (Sweden), Stockholm University, the University of Kentucky, Brookhaven National Laboratory, Massachusetts General Hospital, Harvard University and Brown University. Sponsored by the ALS Therapy Alliance, the agenda included scientific sessions on superoxide dismutase biochemistry in relation to ALS, mechanisms of altered RNA processing in neurodegeneration, animal models of ALS, and novel therapeutic approaches to ALS. Presentations included ground-breaking studies by graduate students and postdoctoral fellows and a special session allowed time for the scientists and students to interact directly with individuals living with ALS.

PROJECT: Small-molecule HTS for SOD1-mediated ALS

Investigator: Osman Bilsel, Ph.D.
University of Massachusetts Medical School, United States

Co-Investigator: Jill Ann Zitzewitz, Ph.D.

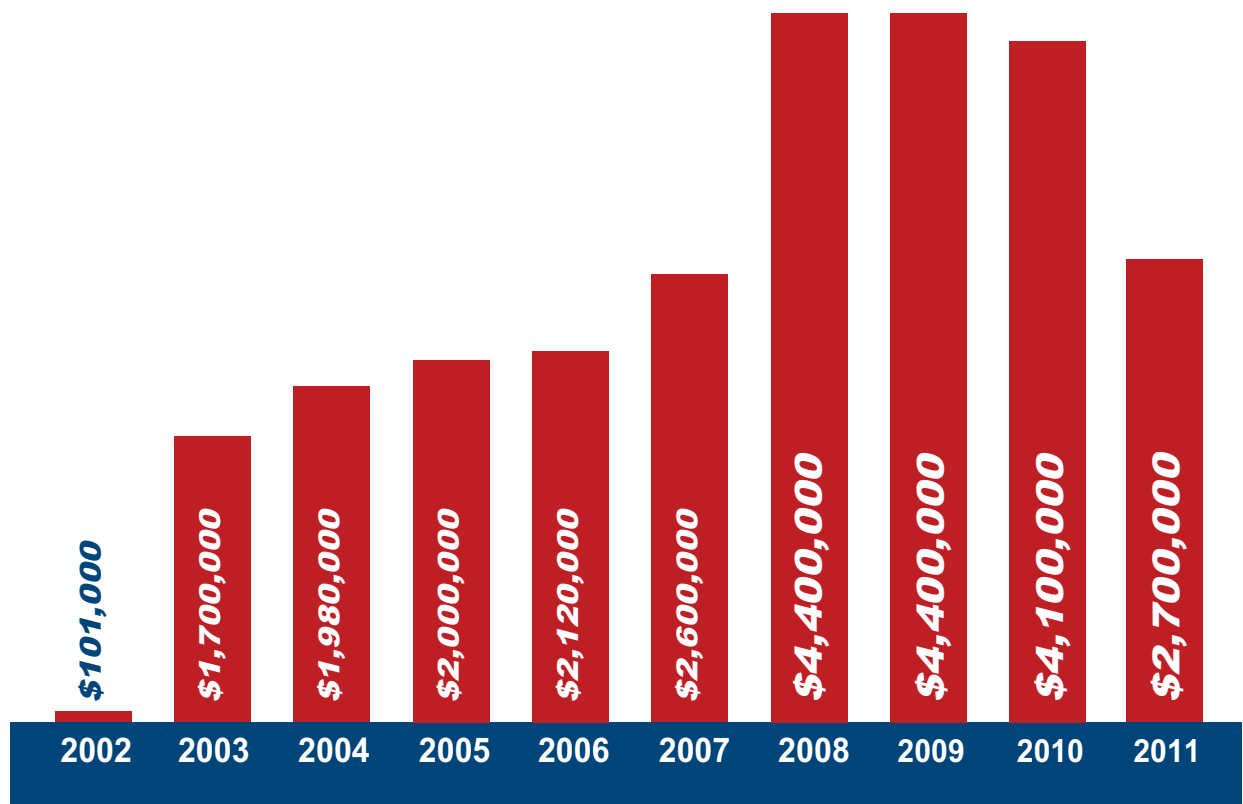
Amyotrophic lateral sclerosis (ALS) is the most common adult motor neuron disease with an average disease duration of less than five years. There is currently only one FDA approved therapeutic, providing a modest increase in average life expectancy. This proposal is aimed toward meeting the need for a small-molecule therapeutic for ALS by performing a high-throughput screen (HTS) that targets the dimeric protein superoxide dismutase (SOD1). Mutations in the gene for this protein have been implicated in approximately 25% of familial ALS (fALS) cases. Although the mechanism of toxicity in fALS is not completely understood, the toxicity is increasingly attributed to the monomeric forms of SOD1. Biophysical studies on disease causing forms of human SOD1 demonstrate that destabilization of the native dimeric form relative to the monomers (folded or unfolded) is a common property. One strategy toward a therapeutic for ALS is to use small molecules to shift the monomer-dimer equilibrium to favor the native dimer and minimize the population of potentially toxic monomeric species. This approach has shown promise in a computer-based screen by the Lansbury/Ray lab.

Our experimental HTS assay is unique in its ability to selectively detect the shift in the monomer-dimer equilibrium upon binding of a small molecule, a sensitivity afforded by a custom fluorescence lifetime-based instrument that offers sensitivity beyond what is commercially available. We anticipate these studies to progress to a larger scale screen that will identify and optimize lead compounds that may ultimately identify drugs that slow the progression of ALS.

HOPE for Tomorrow

By stimulating new ALS research projects, the ALS Therapy Alliance partnership with CVS/pharmacy has provided the ALS community with renewed hope that meaningful ALS treatments will be discovered.

How this fundraising campaign has grown over the years:





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16 Oakland Avenue
Needham, MA 02492-3150
www.alstherapyalliance.org